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ION-PAIR EXTRACTION OF SOME CINCHONA ALKALOIDS WITH VARIOUS CHIRAL ORGANIC ANIONS

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Studies on the Solvent Extraction of the Chiral Ion-pair between Some Cinchona Alkaloids and Acid Derivertives of Camphor

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Two pairs of cinchona alkaloids, the quinine/quinidine and cinchonine/cinchonidine, are extracted by ion-pair formation with some anions of camphor derivertives. The extraction behaviours are examined, and the differences between the two isomers are compared. These alkaloids are extracted into chloroform and 1,2-dichloroethane in the pH range 4 - 7 as the 1:1 ion-pair with the chiral anions. The relationship between the distribution ratio of the ion-pair and pH is discussed. In the pH range between the pK_{a1} and pK_{a2} values of cinchona alkaloids, the extraction constants are determined, and the differences caused by the effect of substituents of cinchona alkaloids and counter ions are examined. The solvent effect are also studied.

Keywords Stereoselectivity, cinchona alkaloid, acid derivertive of camphor, chiral ion-pair

Several investigations for the optical resolution of isomers have been reported by using gas and liquid chromatographic methods.[1-4] However, very little investigations has known about the interaction between solid phase and the solute in mobile phase, because the attention has been focused on the preparation of chiral solid phases that can bind the various enantiomeric forms with different strength.[5-7] Also, there are only a few reports on the aspect of stereoselectivity in liquid-liquid extraction although it is one of simplest separation procedure in analytical chemistry. One of the main reasons may be that the effect of steric hindrance between optical isomers seems very unlikely to appear as a difference in distribution ratios.

In the previous study[8], the author had discussed the diastereomeric separation of the ion-pair extraction between some cinchona alkaloids (two pairs of cinchona alkaloids, the quinine/quinidine and cinchonine/cinchonidine) and some chiral organic acids such as N-acetyl amino acids. The extraction constants of the ion-pair with quinidine was always greater than that of quinine in each organic acid so far examined. Similarly, the extraction constants with cinchonine was greater than that of cinchonidine almost examined. These differences of the extraction constant ratio from 1.3 to 2.5 have been obtained. Also, in the previous study, it was

confirmed that the differences of the log D values obtained by the ion-pair extraction between cinchona alkaloids, such as quinine and quinidine, and achiral counter anion of perchlorate were hardly obserbed. Consequently, in order to achieve more effective diastereomeric separation of optical isomers by ion-pair extraction, it seems to be necessary to employ some chiral counter anions.

In the present study, two pairs of cinchona alkaloids, the quinine/quinidine and cinchonine/cinchonidine, are extracted with some acid derivatives of camphor in order to examine the effect of substituent. The effect of (+)- and (-)-form of cinchona alkaloids and counter anions are also studied.

EXPERIMENTAL

Apparatus and reagents

The Hitachi Model 556 double-beam spectrophotometer used was equipped with a cell holder coupled with a Komatsu-Yamato Model CTR-220 thermostated circulator. Extraction were done with a Taiyo Model M-100T waterbath incubator. A Hitachi-Horiba Model F-7 II pH meter with a glass electrode was used to measure the pH of the aqueous phases after extraction.

Quinine and quinidine solutions (0.01M) were pre-

pared by dissolving 0.3244 g of pure quinine or quinidine in 100 ml of diluted sulphurric acid. Cinchonine and cinchonidine (0.2944 g) were also dissolved in 100 ml of diluted sulphuric acid to prepare 0.01 M solutions. Buffer solutions were prepared by adjusting a mixture containing 0.3 M potassium dihydrogenphosphate and 0.1 M sodium tetraborate to various pH with 0.5 M sulphuric acid or 1 M sodium hydroxide. All other reagents and solvents used were of analytical-reagent grade.

Extractions

Extractions were done in 50-ml test tubes with equal volumes (10 ml) of aqueous and organic phase. The aqueous phase, consisting of a 2.5×10^{-4}M cinchona alkaloid solution, a buffer solution and 2.5×10^{-3}M organic acid, was shaken for 15 min with chloroform or 1,2-dichloroethane in the water bath thermostated at 25 $\pm$ 0.1 °C.

The distribution ratios were calculated from measurements of the absorbances of the organic layer. Absorbances were measured at 333 nm for quinine and quinidine, and at 315 nm for cinchonine and cinchonidine in both chloroform and 1,2-dichloroethane.

RESULTS AND DISCUSSION

The camphor compounds examined as the counter anion were 10-camphorsulfonic acid [(+) and (-)], 3-bromo-

camphor-8-sulfonic acid [(+) and (-)] and camphor-carboxylic acid [(+) and (-)]. These camphor compounds are,of course, optically active reagents possessing two asymmetric carbon atoms in respective molecules.

The acidity constant, pK_a, of camphorcarboxylic acid, found by titration, was 3.72. This value was used later for calculating the concentration of the counter anion at various pH values. Also, 10-camphorsulfonic acid and 3-bromocamphor-8-sulfonic acid seem to be completely dissociated and exists solely as a singly charged anion.

Also, as shown in previous work[8], the pH dependence of the distribution ratio, D_{Q*}, for cinchona alkaloids with various counter anions should be considered as the true distribution ratio, $D_{Q*}-D_Q$, because the distribution ratios, D_{Q*}, include the distribution ratios of the cinchona alkaloids themselves, D_Q. Consequently, the true distribution ratios, $D_{Q*}-D_Q$, of cinchona alkaloids should be considered. Figure 1 shows the logarithmic plots of $(D_{Q*}-D_Q)$ against the counter ion concentration in the case of cinchonine with (1R)-(-)-10-camphorsulfonic acid and of quinine with (+)-3-bromocamphor-8-sulfonic acid at pH values below and above pK_{a1}. These straight lines have unit slope, hence the cinchona alkaloid/counter anion ion-pair can be assumed to have a 1:1 composition.

When the pH region of aqueous solution is divided

into three regions in the same way as described in previous work[8], the logarithmic true distribution ratios can also be written as follows;

(i) $pH < pK_{a1} < pK_{a2}$

$$\log(D_{Q*}-D_Q) = \log K_{ex} + \log[X^-] - pK_{a1} + pH \qquad (1)$$

(ii) $pK_{a1} < pH < pK_{a2}$

$$\log(D_{Q*}-D_Q) = \log K_{ex} + \log[X^-] \qquad (2)$$

(iii) $pK_{a1} < pK_{a2} < pH$

$$\log(D_{Q*}-D_Q) = \log K_{ex} + \log[X^-] + pK_{a2} - pH \qquad (3)$$

where $K_{ex} = [HQ^+ \cdot X^-]_o/[HQ^+][X^-]$. In these equations, the concentration of the counter anion, $\log[X^-]$, is;

$$\log[X^-] = \log[HX]_{tot} - pK_a - \log([H^+] + K_a)$$

where $[HX]_{tot}$ is the total uncomplexed concentration, and K_a is the acidity constant of the organic acid, HX, determined previously by titration. Equations (1) - (3) indicate that the plots of the logarithmic true distribution ratio against pH should show straight lines with slopes of +1 in the pH region below the pK_{a1} value and slopes of -1 in the pH region above the pK_{a2} value, but should be independent of pH in the pH region between the pK_{a1} and pK_{a2} values.

Figure 2 shows the pH dependence of the logarithmic true distribution ratio, $\log(D_{Q*}-D_Q)$, of cinchona alkaloids with some anions of camphor derivatives in chloroform. Figure 3 shows, also, the results in 1,2-dichloro-

ethane. These plots show the straight lines with slopes of +1 in the pH region below pK_{a1} and changing to approximately straight lines with zero slope for pH values higher than pK_{a1}. These results correspond to the theoretically derived expressions.

The logarithmic extraction constants for the ion-pair between the cinchona alkaloids and the chiral anions tested were calculated from Eqn.2. The results are presented in Table 1. The differences of the logarithmic extraction constants, $\Delta\log K_{ex}$, for the quinine/quinidine and cinchonine/cinchonidine systems are also given in Table 1. The extraction constants with camphorcarboxylic acid in chloroform could not evaluate because the plots of pH dependence of $\log(D_{Q*}-D_Q)$ had varied widely in the pH region over pK_{a1}.

As can be seen in Table 1, obvious differences in the extraction constants were obtained for the two isomers with some of the anions of camphor derivatives used. The extraction constants of the ion-pair with quinidine were always greater than that of quinine in each solvent so far examined, regardless of the kind of the counter anion. Similarly, the extraction constants with cinchonine were always greater than that of cinchonidine. The differences of the logarithmic extraction constants, $\Delta\log K_{ex}$, for the cinchonine/cinchonidine system were almost greater than that for the

quinine/quinidine system. These results coincide with that obtained with amino acids as shown in the previous work[8]. It is possible to mention from this results that the isomers of quinine and quinidine which possess the methoxyl group in the molecule have less stereo-selectivity than the isomers of cinchonine and cinchonidine which have no methoxyl groupe. On the other hand, as shown in Table 1, the differences of the extraction constants between camphor isomers used as counter anions were hardly observed despite the kind of cinchona alkaloids.

The extractability of the ion-pair in chloroform was superior to that in 1,2-dichloroethane. This result may be caused by the differences of the tendency of the ion-pair formation in organic solvents. Also, there were no differences in the $\Delta\log K_{ex}$ values between two solvents so far examined in this study.

As shown in Table 1, the ion-pair with various kind of anions of camphor derivertives showed the various extraction constants. Generally, the extractability increased in the order bromocamphor sulfonic acid > camphorcarboxylic acid > camphorsulfonic acid. However, the $\Delta\log K_{ex}$ values with various chiral anions could not obtain the clear regularity by the effect of substituent.

The (+)-formed optical isomers such as quinidine

and cinchonine seem to be more extractable than the (-)-formed isomers such as quinine and cinchonidine, as mentioned above, however, more clear regularity on the chiral selectivity was not obtained by pairing with (+)- or (-)-formed anions of camphor derivertives.

From the results obtained in the present and the previous work[8], it is possible to concider that the selectivity between two isomers obtained by ion-pair extraction procedure is caused mainly by following two reasons. (1) In the aqueous solution, the cations of the cinchona alkaloids exist as the aquo-ions having their slightly different solvation energy. When these aquo-ions are extracted into organic phases, the extractability of the aquo-ions must be influenced in accordance with the small differences of their solvation energy in both phases. (2) The effect of steric hindrance caused by the ion-pair formation between solvated cations and solvated counter anions in the organic solvents play a important role in chiral selectivity.

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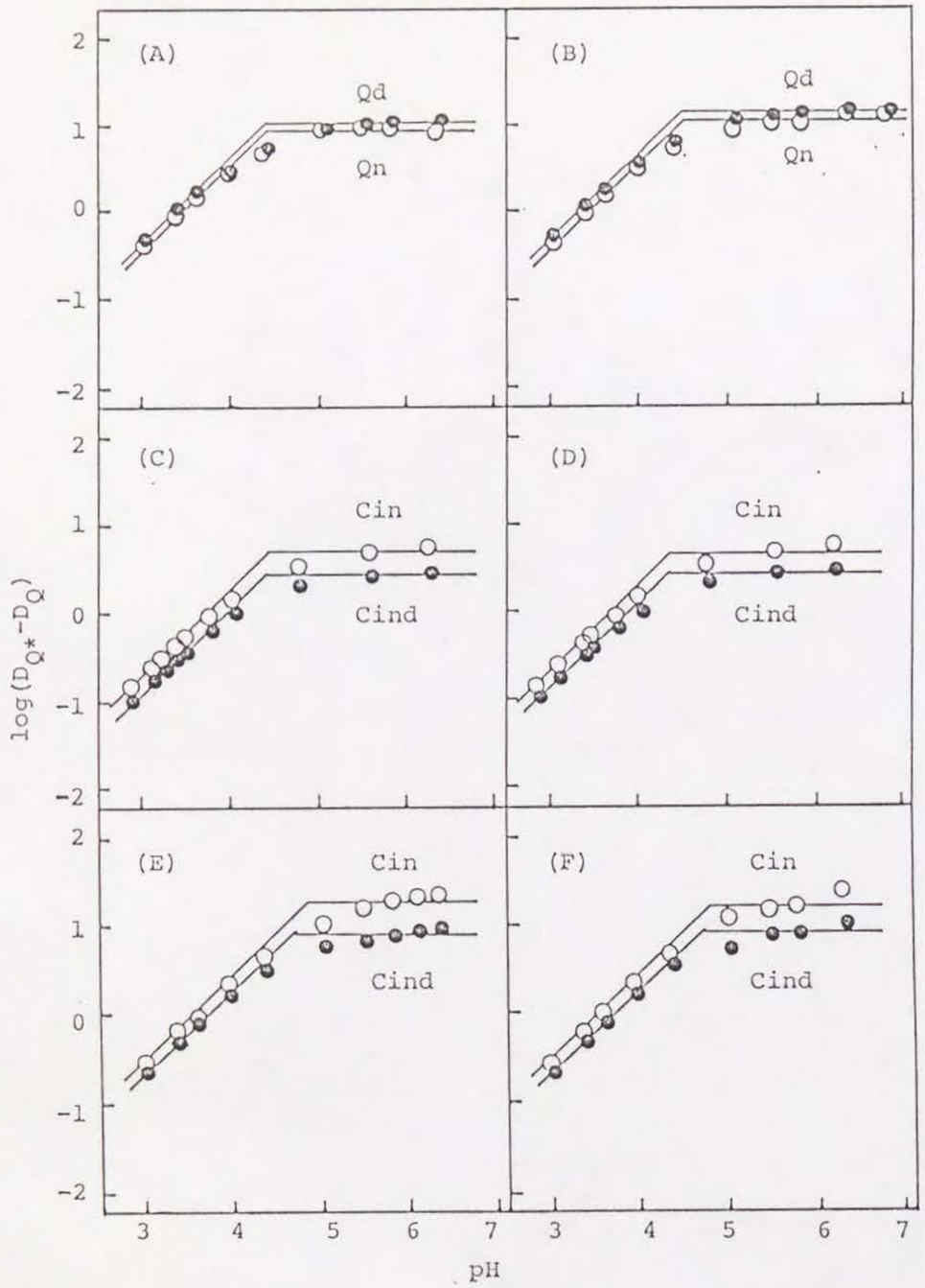

Fig.2 pH dependence of the logarithmic true distribution ratios of cinchona alkaloids in the presence of different counter anions. (Chloroform)
(A) (+)-3-bromocamphor-8-sulfonic acid; (B) (-)-form;
(C) (1S)-(+)-10-camphorsulfonic acid; (D) (-)-form;
(E) (+)-3-bromocamphor-8-sulfonic acid; (F) (-)-form.
Qn: quinine, Qd: quinidine, Cin: Cinchonine, Cind: Cinchonidine

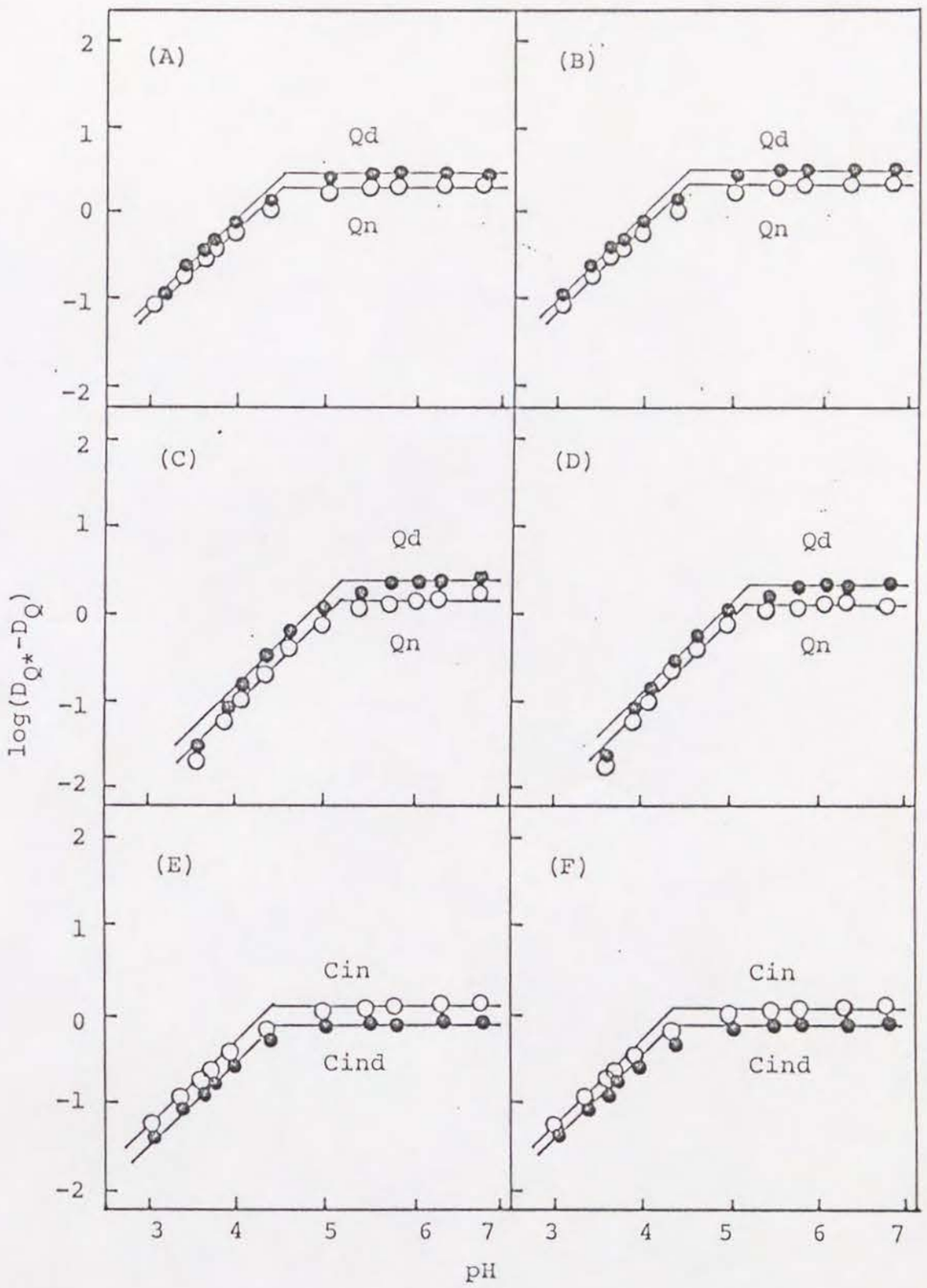

Fig.3 pH dependence of the logarithmic true distribution ratios of cinchona alkaloids in the presence of different counter anions. (1,2-Dichloroethane)
(A) (+)-3-bromocamphor-8-sulfonic acid; (B) (-)-form;
(C) (+)-camphorcarboxylic acid; (D) (-)-form;
(E) (+)-3-bromocamphor-8-sulfonic acid; (F) (-)-form.
Qn: quinine, Qd: quinidine, Cin: Cinchonine, Cind: cinchonidine

Table 1 Extraction Constants for $[HQ^+ \cdot X^-]$

(A) Chloroform

	Quinine	Quinidine	$\Delta \log K_{ex}$	Cinchonine	Cinchonidine	$\Delta \log K_{ex}$
(1)	3.18	3.31	0.13	3.25	3.00	0.25
(2)	3.25	3.35	0.10	3.26	3.03	0.23
(3)	3.41	3.53	0.12	3.75	3.41	0.34
(4)	3.41	3.52	0.11	3.72	3.52	0.20

(B) 1,2-Dichloroethane

(1)	2.40	2.57	0.17	2.15	1.92	0.23
(2)	2.44	2.52	0.08	2.10	1.99	0.11
(3)	2.90	3.05	0.15	2.63	2.45	0.18
(4)	2.90	3.05	0.15	2.63	2.46	0.17
(5)	2.70	2.90	0.20	2.57	2.38	0.19
(6)	2.71	2.91	0.20	2.62	2.33	0.29

(1): (1S)-(+)-10-Camphorsulfonic acid
(2): (1R)-(-)-10-Camphorsulfonic acid
(3): (+)-3-Bromocamphor-8-sulfonic acid
(4): (-)-3-Bromocamphor-8-sulfonic acid
(5): (+)-Camphorcarboxylic acid
(6): (-)-Camphorcarboxylic acid

[Cinchona alkaloid]=2.5 X 10^{-4}M, [HX]=2.5 X 10^{-3}M.

Fig.1 Logarithmic plots of $(D_{Q^*}-D_Q)$ vs. [(1R)-(-)-10-camphorsulphonic acid] for cinchonine (A) and [(+)-3-bromocamphor-8-sulfonic acid] for quinine (B). pH: (A) (1)4.0 (2) 5.7, (B) (1)4.1 (2)5.8.

Fig.2 pH dependence of the logarithmic true distribution ratios of cinchona alkaloids on the presence of different counter anions. (Chloroform)
(A) (+)-3-bromocamphor-8-sulfonic acid; (B) (-)-form;
(C) (1S)-(+)-10-camphorsulfonic acid; (D) (-)-form;
(E) (+)-3-bromocamphor-8-sulfonic acid; (F) (-)-form.
Qn: quinine, Qd: quinidine, Cin: cinchonine, Cind: cinchonidine

Fig.3 pH dependence of the logarithmic true distribution ratios of cinchona alkaloids in the presence of different counter anions. (1,2-Dichloroethane)
(A) (+)-3-bromocamphor-8-sulfonic acid; (B) (-)-form;
(C) (+)-camphorcarboxylic acid; (D) (-)-form;
(E) (+)-3-bromocamphor-8-sulfonic acid; (F) (-)-form.
Qn: quinine, Qd: quinidine, Cin: cinchonine, Cind: cinchonidine

Stereoselectivity in Adduct Formation of Quinine and Quinidine with α-Acyl-d-camphorato Copper(II)

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The formation constants of the adducts formed between quinine or quinidine and bis(3-trifluoroacetyl-d-camphorato)copper(II), bis(3-heptafluorobutyryl-d-camphorato)copper(II), or bis(3-pivaloyl-d-camphorato)copper-(II) have been determined spectrophotometrically in carbon tetrachloride, benzene, toluene, *m*-xylene, chloroform and 1,2-dichloroethane. The formation constant of quinine adduct is always greater than that of quinidine one in each bis(3-acyl-d-camphorato)copper(II)–organic solvent system so far examined.

Keywords Stereoselectivity, cinchona-alkaloid, adduct formation constant, α-acyl-d-camphorato Cu(II) chelate

Copper(II) complexes of β-diketones are known to coordinate with various neutral ligands such as phosphorus esters, amines and heterocyclic N-bases.[1-5] This adduct-formation reaction plays an important role in the synergistic effect for solvent extraction.[6-9]

The author has made a study of stereoselectivity by solvent extraction method, wherein some cinchona-alkaloids are extracted by ion pair formation with some optically active organic acids.[10] The extraction constant of the ion pair with quinidine was always greater than that of quinine in each organic solvent so far examined, and differences of the extraction constant ratio from 1.3 to 2.5 have been obtained.

α-Acyl-d-camphorato metal chelates are known to be used for the determination of enantiomeric purity by NMR spectroscopy[11,12], and are also expected to be important as the stationary phase of chromatography to separate the optically active substances.[13-15]

In the present work, the stereoselectivity between quinine and quinidine was studied by using some α-acyl-d-camphorato copper(II) chelates, and the formation constants of the mono-adduct were determined spectrophotometrically in several organic solvents. The α-acyl-d-camphorato copper(II) chelates examined here are bis(3-trifluoroacetyl-d-camphorato)copper(II), Cu(facam)$_2$, bis(3-heptafluorobutyryl-d-camphorato)copper(II), Cu(hfbc)$_2$, and bis(3-pivaloyl-d-camphorato)-copper(II), Cu(picam)$_2$, which are optically active substances for possessing four asymmetric carbon atoms in a molecule.

Experimental

Apparatus and reagents

Spectrophotometric measurements were carried out using a Hitachi Model 556 double-beam spectrophotometer with a thermostated cell holder coupled with a Komatsu–Yamato Model CTR-220 thermostated circulator.

Quinine and quinidine stock solutions (0.01 M) were freshly prepared each week by dissolving 0.3244 g of quinine and quinidine (Nakarai Chem.) in 100 ml each of the organic solvents examined here, and working solutions were prepared by accurate dilution of the stock solutions.

3-Trifluoroacetyl-d-camphor (Hfacam) was synthesized from ethyltrifluoroacetate and d-camphor using a procedure similar to that described by Kopecky[16], 3-pivaloyl-d-camphor (Hpicam) was synthesized from pivaloyl chloride and d-camphor using a procedure similar to that described by McCreary[17], 3-heptafluorobutyryl-d-camphor (Hhfbc) was used a product of Aldrich Chem. The analytical data of (Hfacam) and (Hpicam) are as follows (calculated values are shown in parentheses):

Hfacem	C:	57.97	(58.06)
	H:	6.10	(6.09)
Hpicam	C:	76.21	(76.22)
	H:	10.36	(10.24)

Each of the copper complexes: Cu(facam)$_2$, Cu(hfbc)$_2$ and Cu(picam)$_2$, was prepared by adding an ethanol solution of the ligand to an aqueous solution of copper acetate at 60°C. After cooling, the crystals which precipitated were filtered off. These products were recrystallized from benzene and then sublimed three times *in vacuo* at 160°C.

Calculation of formation constants

The formation constant K_1 of the mono-adduct was calculated by the following equations.[18,19] The reaction

of a Lewis base, B, with an α-acyl-d-camphorato Cu(II), CuX_2, is of the type given below:

$$CuX_2+B \overset{K_1}{\rightleftharpoons} CuX_2B. \quad (1)$$

The formation constant, K_1 of the reaction is defined as:

$$K_1 = \frac{[CuX_2B]}{\{C_A-[CuX_2B]\}\{C_B-[CuX_2B]\}} \quad (2)$$

where C_A and C_B are the initial concentrations of CuX_2 and B, respectively, and $[CuX_2B]$ is the equilibrium concentration of the mono-adduct, CuX_2B. The value ΔA is given as follows:

$$\Delta A = A-A_0 = (\varepsilon_2-\varepsilon_1)[CuX_2B] \quad (3)$$

where A and A_0 are the absorbances at a chosen wavelength in the presence and absence of B, and ε_1 and ε_2 are the extinction coefficients of CuX_2 and CuX_2B, respectivey. Equations (2) and (3) give equation (4):

$$\frac{C_AC_B}{\Delta A} = \frac{1}{(\varepsilon_2-\varepsilon_1)}[C_A+C_B-\frac{\Delta A}{(\varepsilon_2-\varepsilon_1)}]+\frac{1}{(\varepsilon_2-\varepsilon_1)K_1}. \quad (4)$$

The least-squares method (SALS program)[20] was applied to obtain the best K_1 and ε_2 values at the same time. In order to obtain suitable initial values of K_1 and ε_2, the following modified Benesi equation[15] was used:

$$\frac{C_A}{\Delta A} = \frac{1}{(\varepsilon_2-\varepsilon_1)K_1}\times\frac{1}{C_B}+\frac{1}{(\varepsilon_2-\varepsilon_1)}. \quad (5)$$

Results and Discussion

The spectrum of $Cu(facam)_2$ exhibited two maxima at 574 and 680 nm, $Cu(hfbc)_2$ at 565 and 680 nm (Fig. 1(a)), and $Cu(picam)_2$ exhibited a maximum at 660 nm in benzene. However, these spectra slightly differ in the organic solvents examined. The spectral features resemble those of bis(acetylacetonato)copper-(II) and bis(trifluoroacetylacetonato)copper(II) with a square-planner symmetry.[21] The spectral change of $Cu(hfbc)_2$ in benzene caused by the addition of quinine at 25°C is shown in Fig. 1. When the concentration ratio of quinine to $Cu(hfbc)_2$ was in the range 0 – 1.6, a clear isosbestic point was observed. The ΔA values at 680 nm, $A-A_0$, gradually approached to a constant value with the increase of the quinine concentration, as shown in Fig. 1, indicating the formation of a mono-adduct. The isosbestic point disappeared gradually with the further increase of the quinine concentration. This may indicate the formation of a rather unstable 2:1 or higher complex. The spectral change of $Cu(hfbc)_2$ due to quinidine is almost the same as that shown in Fig. 1.

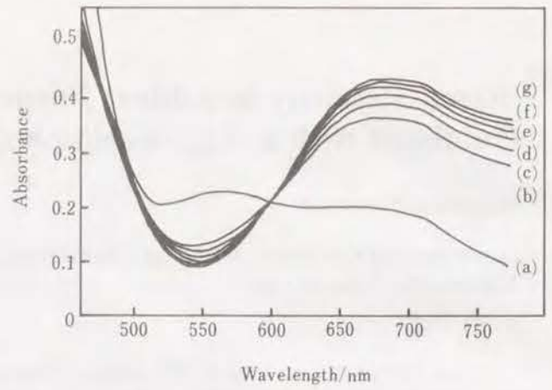

Fig. 1 Spectral change of $Cu(hfbc)_2$ in benzene caused by the addition of quinine. $C_A=5\times10^{-3}$ M; ratio of C_B/C_A: (a) 0.0, (b) 0.6, (c) 0.8, (d) 1.0, (e) 1.2, (f) 1.4, (g) 1.6.

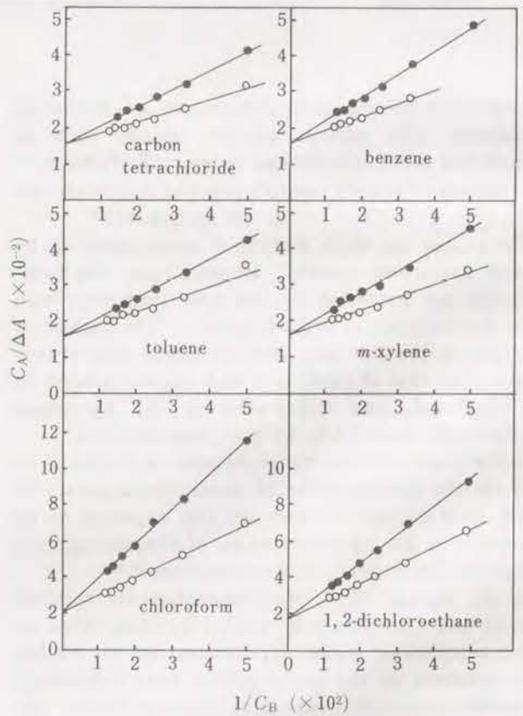

Fig. 2 Plots of Eq. (5) for the adduct formation of $Cu(hfbc)_2$ with quinine and quinidine: ○, quinine; ●, quinidine.

In order to calculate the initial values of K_1 and ε_2, the linear plots of Eq.(5), $C_A/\Delta A$ *vs.* $1/C_B$ were made. Figure 2 shows the results of $Cu(hfbc)_2$ in six organic solvents; carbon tetrachloride, benzene, toluene, *m*-xylene, chloroform and 1,2-dichloroethane. As shown in Fig. 2, good linear relationships were obtained in all the organic solvents examined here. The initial values

of K_1 and ε_2 were calculated from the slopes and the *y*-intercepts in Fig. 2. The differences of the slopes between quinine and quinidine correspond with the differences of their K_1 values from Eq.(5). Good linear relationships were obtained for $Cu(facam)_2$ chelate in all organic solvents tested here. However, the adduct-formation reaction with $Cu(picam)_2$ did not give any reproducible data in some of the organic solvents tested here. The $Cu(picam)_2$ adducts appeared to be light-sensitive, and the solubility in some organic solvents appeared to be lower than that in $Cu(hfbc)_2$ and $Cu(facam)_2$ adducts.

The K_1 values calculated using the initial values obtained from Fig. 2 are summarized in Table 1. The linear plots of Eq.(4), $C_AC_B/\Delta A$ *vs.* $C_A+C_B-\Delta A/(\varepsilon_2-\varepsilon_1)$, are shown in Fig. 3. The solid lines are drawn on the basis of the calculated K_1 and ε_2 values. The agreement of the plots with the solid lines supports the validity of the calculated K_1 and ε_2 values.

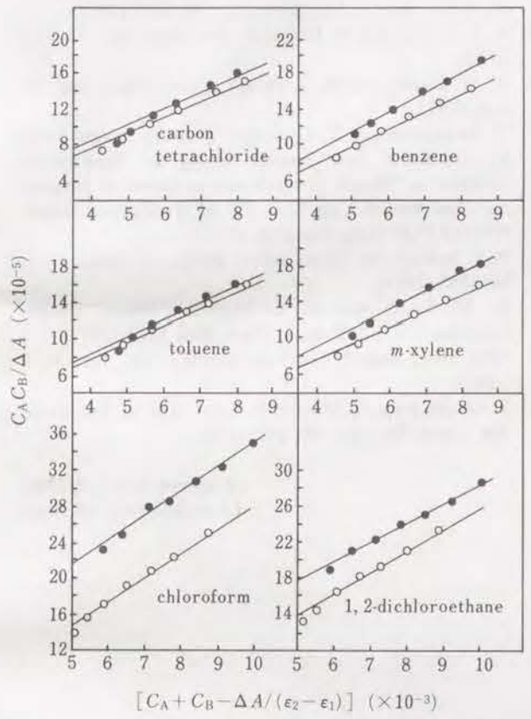

Fig. 3 Plots of Eq. (4) for the adduct formation of $Cu(hfbc)_2$ with quinine and quinidine: ○, quinine; ●, quinidine.

As shown in Table 1, the K_1 values of quinine ($K_{1,A}$) and quinidine ($K_{1,B}$) were remarkably different, except for the values for $Cu(picam)_2$ chelate. The K_1 values of quinidine adducts were smaller than those of quinine ones in all the adduct-formation reactions examined here, whereas the extraction constants of ion pairs with chiral organic acids were reversed, as shown in the previous study.[10]

The structure of bis(β-diketonato)copper(II) is a square-planer form, and the mono-adduct with quinine or quinidine seems to form a square-pyramidal structure. When the rigid and bulky α-acyl-d-camphorato copper(II) chelates form the mono-adducts with the bulky ligands such as quinine and quinidine, the steric effect should be remarkable.

Both quinine and quinidine molecules possess two N-atoms at the quinoline ring and at the tertiary amine. It seems that a N-atom at the quinoline ring does not coordinate to a Cu-atom in the copper(II) complex but at the tertiary amine between the two N-atoms of quinine and quinidine because the basicity of a N-atom at the quinoline ring is smaller than that of the tertiary amine.[22,23] When the K_1 values of pyridine adducts[1,2,24] with the copper(II) β-diketonato chelates are compared with the present data, the very small values are found. One of the reasons for this result may be that the basicity of pyridine N-atom is smaller than that of tertiary amine.

As shown in Table 1, the K_1 values increased in the order $Cu(hfbc)_2$>$Cu(facam)_2$>$Cu(picam)_2$ except in *m*-xylene. This suggests the differences of the electron-withdrawing effect among the groups of CF_3, C_3F_7 and $C(CH_3)$.

The formation constants of the adducts increased roughly in the order carbon tetrachloride>benzene≃toluene≃*m*-xylene>chloroform≃1,2-dichloroethane, which agreed with the reverse order of the dielectric constants. The stability constants of the $Cu(picam)_2$ adducts were obtained only in toluene and chloroform because their solubility and stability in other solvents were low.

Table 1 Formation constants of mono-adducts (10^3 M^{-1})

Solvent	$Cu(facam)_2$			$Cu(hfbc)_2$			$Cu(picam)_2$		
	$K_{1,A}$	$K_{1,B}$	$K_{1,A}/K_{1,B}$	$K_{1,A}$	$K_{1,B}$	$K_{1,A}/K_{1,B}$	$K_{1,A}$	$K_{1,B}$	$K_{1,A}/K_{1,B}$
Carbon tetrachloride	12.65	5.91	2.14	16.70	2.26	7.39			
Benzene	6.71	3.21	2.09	9.24	3.65	2.53			
Toluene	7.33	3.99	1.84	9.59	2.10	4.57	3.15	2.50	1.26
m-Xylene	7.92	1.59	4.98	5.89	2.78	2.12			
Chloroform	0.84	0.47	1.79	1.65	0.32	5.16	1.64	1.39	1.18
1,2-Dichloroethane	1.05	0.41	2.56	1.33	0.30	4.43			

$K_{1,A}$, quinine; $K_{1,B}$, quinidine.

The ratios of formation constants for the mono-adducts, $K_{1,A}/K_{1,B}$, which gives a measure of stereoselectivity of the chiral copper(II) chelate for quinine and quinidine, are listed in Table 1. The ratios increased substantially in the order $Cu(hfbc)_2$>$Cu(facam)_2$>$Cu(picam)_2$, which agreed with the order of K_1 values. The $K_{1,A}/K_{1,B}$ ratio for $Cu(hfbc)_2$ varied from 2.12 in *m*-xylene to 7.39 in carbon tetrachloride.

However, the reason for the stereoselectivity between quinine and quinidine is not clear from the results obtained in this study. It is necessary to investigate and to discuss this problem more from the standpoint of the stereochemistry.

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